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EXAMINER	
KUBELIK, ANNE R	

ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 11/14/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/923,844	BAO ET AL.	
	Examiner	Art Unit	
	Anne R. Kubelik	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *1-14, 23 and 27-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-22 and 24-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *8/7/01* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's amendments filed 16 June 2003 have been entered. Claims 1-34 are pending. Claims 1-14, 23 and 27-34 remain withdrawn from consideration as being drawn to nonelected inventions. Claims 15-22 and 24-26 are examined to the extent they read on SEQ ID NO:3.

2. The abstract is not descriptive of the instant invention, which is a lipid transfer protein-encoding nucleic acid from sunflower, constructs and vectors comprising the nucleic acids, cells, plants and seeds comprising the constructs, and methods of using the constructs to create or enhance disease resistance in a plant. A new abstract is required that is clearly indicative of the invention to which the claims are directed. The abstract of the disclosure should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The objection is repeated for the reasons of record as set forth in the Office action mailed 13 March 2003. Applicant's arguments filed 16 June 2003 have been fully considered but they are not persuasive.

Applicant urges that they have amended to abstract to be indicative of the invention to which the claims are directed (response pg 10).

This is not found persuasive because the abstract still mentions lipid transfer proteins, to which the instant claims are not drawn.

3. The title of the invention is still not descriptive of the instant invention, as above. A new title is required that is clearly indicative of the invention to which the claims are directed. Note that titles can be up to 500 characters long.

The objection is repeated for the reasons of record as set forth in the Office action mailed 13 March 2003. Applicant's arguments filed 16 June 2003 have been fully considered but they are not persuasive.

Applicant urges that the title has been amended to be descriptive of the instant invention (response pg 10).

This is not found persuasive because the instant nucleic acid is from sunflower.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. The amendment filed 16 June 2003 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material that is not supported by the original disclosure is as follows: The changing the database from "GenBank to "SwissProt" and changing "A64431" to "O64431 and "Q81135" to "O821135" in the two paragraphs starting on pg 57, line 19. There is no support in the originally filed specification for these changes.

Applicant is required to cancel the new matter in the reply to this Office Action.

Withdrawn Rejections

6. The rejection of claims 15-21 and 24-26 under 35 U.S.C. 102(b) as being anticipated by Kragh et al (WO 95/11306) is withdrawn in light of Applicant's amendment to the claims.

7. The rejection of claims 15-22 and 24-26 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in such a way

as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is withdrawn in light of Applicant's statement that all restrictions upon availability to the public will be irrevocably removed upon granting of the patent.

Claim Rejections - 35 USC § 112

8. Claims 15-22 and 24-26 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The rejection is modified from the rejection set forth in the Office action mailed 13 March 2003. Applicant's arguments filed 16 June 2003 have been fully considered but they are not persuasive.

The claims are broadly drawn to multitude of nucleic acids that hybridize to a nucleic acid with 95% identity to SEQ ID NO:3 or to a nucleic acid that encodes SEQ ID NO:4 or to nucleic acids that are lipid transfer protein-encoding nucleic acids with 95% identity to SEQ ID NO:3. The claims are also drawn to constructs and vectors comprising the nucleic acids, cells, plants and seeds comprising the constructs, and methods of using the constructs to create or enhance disease resistance in a plant.

The instant specification, however, only provides guidance for isolation of lipid transfer protein (LTP) cDNA by sequencing cDNAs of RNAs expressed in sunflower in response to *Sclerotinia* infection and by isolating full-length cDNAs by RACE-PCR (example 1); and isolation of the LTP promoter by PCR (example 1). The cDNA is SEQ ID NO:3, which encodes

SEQ ID NO:4; the promoter is SEQ ID NO:6. The specification also provides guidance for Northern analysis showing that LTP transcripts were induced by *Sclerotinia* infection (examples 2 and 3); and general guidance for transformation of sunflower and maize with a construct comprising SEQ ID NO:3 (examples 4 and 5).

The instant specification fails to provide guidance for lipid transfer protein-encoding nucleic acids with 70% identity to SEQ ID NO:3, nucleic acids comprising at least 16 contiguous nucleotides of a nucleic acid that encodes SEQ ID NO:4, or nucleic acids that hybridize to the latter nucleic acid.

The instant specification fails to provide guidance for construction or isolation of the claims nucleic acids. For example, the specification fails to provide guidance for the exact hybridization or amplification conditions and probes/primers to use in isolation of nucleic acids other than SEQ ID NO:3.

The specification on pg 23, lines 4-18, suggests making variant nucleic acids by making conservative substitutions in the encoded protein. However, making such "conservative" substitutions (*e.g.*, substituting one polar amino acid for another, or one acidic one for another) does not produce predictable results. Lazar et al (1988, Mol. Cell. Biol. 8:1247-1252) showed that the "conservative" substitution of glutamic acid for aspartic acid at position 47 reduced biological function of transforming growth factor alpha while "nonconservative" substitutions with alanine or asparagine had no effect (abstract). Similarly, Hill et al (1998, Biochem. Biophys. Res. Comm. 244:573-577) teach that when three histidines that are maintained in ADP-glucose pyrophosphorylase across several species are substituted with the "nonconservative" amino acid glutamine, there is little effect on enzyme activity, while the substitution of one of

those histidines with the "conservative" amino acid arginine drastically reduced enzyme activity (see Table 1). All these mutated proteins, however, would have at least 95% identity to the original protein and the nucleic acids encoding all these mutated proteins would hybridize under high stringency to the nucleic acids encoding the original protein.

Additionally, it is noted that a search of GenBank found no sequences in either the nucleotide or protein databases that matched the GenBank Accession Numbers listed on the originally filed pg 58, lines 4-12 of the specification.

Given the claim breath, unpredictability, and lack of guidance as discussed above, undue experimentation would have been required by one skilled in the art to develop and evaluate lipid transfer protein-encoding nucleic acids with 95% identity to SEQ ID NO:3. SEQ ID NO:3 is Making all possible single amino acid substitutions (thus, substitutions of no more than three nucleotides) in an 97 amino acid long protein like that encoded by SEQ ID NO:3 would require making and analyzing 19^{97} nucleic acids; these nucleic acids would have at least 98.9% identity to SEQ ID NO:2. Claim 1 is drawn to an isolated nucleic acid with 95% identity to SEQ ID NO: 3. SEQ ID NO:3 is 475 nucleotides long. A nucleic acid with 95% identity to SEQ ID NO:3 would have 23 nucleotide substitutions, and could encode a protein with up to 23 amino acid substitutions; this protein would have 76.2% similarity to SEQ ID NO:4. The specification does not describe proteins with 76.2 identity to SEQ ID NO:4.

Lastly, it is not clear what nucleic acids were deposited as Patent Deposit No. PTA-2182.

As the specification does not describe the transformation of any plant with a lipid transfer protein-encoding n nucleic acids that hybridize to a nucleic acid with 95% identity to SEQ ID NO:3 or to a nucleic acid that encodes SEQ ID NO:4 or to nucleic acids that are lipid transfer

protein-encoding nucleic acids with 95% identity to SEQ ID NO:3, undue trial and error experimentation would be required to screen through the myriad of nucleic acids encompassed by the claims and plants transformed therewith, to identify those with enhanced disease resistance, if such plants are even obtainable.

Given the claim breath, unpredictability in the art, undue experimentation, and lack of guidance in the specification as discussed above, the instant invention is not enabled.

Applicant urges that they have provided extensive guidance on pg 10-11 of the specification as to the selection of stringency conditions based on the desired outcome and that probe design is described on pg 25-26 (response pg 11).

This is not found persuasive because pg 10-11 of the specification describes typical hybridization conditions but does not describe the time of the wash. Furthermore, the specification must teach how to make the claimed nucleic acids, not how to find the claimed nucleic acids.

Applicant urges that non-operative embodiments are not claimed; only those with lipid transfer activity are claimed (response pg 12).

This is not found persuasive because the specification does not teach which, of all the multitude of nucleic acids that hybridize to a nucleic acid with 95% identity to SEQ ID NO:3, encode lipid transfer protein.

Applicant urges that Dayhoff et al, which was incorporated by reference into the specification, provides guidance for making amino acid substitutions that do not affect biological activity and that conservative substitutions may be preferable. Furthermore, Applicant urges that Lazar shows that even conservative substitutions dramatically affected one amino acid position,

as would be expected for an amino acid absolutely conserved at that position. Applicant urges that sequence-searching algorithms can be used to identify homology to known proteins (response pg 12-13).

This is not found persuasive. Amino acid conservation does not provide guidance for making amino acid substitutions. Hill et al, cited in the prior Office action, teach that when three histidines that are maintained in ADP-glucose pyrophosphorylase across several species are substituted with the "nonconservative" amino acid glutamine, there is little effect on enzyme activity, while the substitution of one of those histidines with the "conservative" amino acid arginine drastically reduced enzyme activity (see Table 1). Thus, amino acid substitution requires trail and error experimentation, which given the size of the protein encoded by SEQ ID NO:3 would require making and analyzing up to 19^{97} nucleic acids just for single amino acid substitutions. Dayhoff could not be considered because it was not sent.

Applicant urges that the screening out of inoperative species is a common practice in biotechnology and the with guidance in the specification isolation of operative embodiments has a reasonable expectation of success (response pg 13).

This is not found persuasive because the vast number of possible nucleic acids, as discussed above, means that undue experimentation would be required to practice the invention as taught in the specification.

Applicant urges that the numbers provided in the specification are actually SwissProt database accession numbers, not GenBank accession numbers as recited in the originally filed specification. Furthermore, Applicant urges that typographical errors were made in the recitation of some of those numbers (response pg 13).

This is not found persuasive because the amendments introduced new matter into the specification (see above).

Applicant sent copies of these sequence and an alignment of SEQ ID NO:4 with each of them separately and together (response pg 13-14).

This is accepted because even though the percent similarity between SEQ ID NO:4 and each of these sequences is 40-56%, the instant sequence has all the conserved cysteines of lipid transfer proteins.

9. Claims 15-22 and 24-26 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is modified from the rejection set forth in the Office action mailed 13 March 2003. Applicant's arguments filed 16 June 2003 have been fully considered but they are not persuasive.

The claims are broadly drawn to a multitude of nucleic acids that hybridize to a nucleic acid with 95% identity to SEQ ID NO:3 or to a nucleic acid that encodes SEQ ID NO:4 or to nucleic acids that are lipid transfer protein-encoding nucleic acids with 95% identity to SEQ ID NO:3.

In contrast, the specification only describes a coding sequence from sunflower that comprises SEQ ID NO:3. Applicant does not describe other DNA molecules encompassed by the claims, and the structural features that distinguish all such nucleic acids from other nucleic acids are not provided.

Additionally, no description is provided as to the function of the protein encoding by nucleic acids that hybridize to a nucleic acid with 95% identity to SEQ ID NO:3 or to one that encodes SEQ ID NO:4.

Hence, Applicant has not, in fact, described nucleic acids that hybridize to a nucleic acid with 95% identity to SEQ ID NO:3 or to a nucleic acid that encodes SEQ ID NO:4 or to nucleic acids that are lipid transfer protein-encoding nucleic acids with 95% identity to SEQ ID NO:3 within the full scope of the claims, and the specification fails to provide an adequate written description of the claimed invention.

Therefore, given the lack of written description in the specification with regard to the structural and physical characteristics of the claimed compositions, it is not clear that Applicant was in possession of the genus claimed at the time this application was filed.

See *Univ. of California v. Eli Lilly*, 119 F.3d 1559, 43 USPQ 2d 1398 (Fed. Cir. 1997) at pg 1406:

> ... A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus.
> ... the claimed genera of vertebrate and mammal cDNA are not described by the general language of the '525 patent's written description supported only by the specific nucleotide sequence of rat insulin.

Applicant urges that they have given clear guidance for hybridization conditions, as discussed above (response pg 15).

This is not found persuasive because the specification does not describe nucleic acids that hybridize to SEQ ID NO:3 and does not describe the hybridization and wash times. Additionally, no description is provided as to the function of the protein encoding by nucleic acids that hybridize to a nucleic acid with 95% identity to SEQ ID NO:3 or to one that encodes SEQ ID NO:4.

10. Claims 15-22 and 24-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention. Dependent claims are included in all rejections.

Claims 15 and 25 are indefinite in their recitation of "the group consisting of the sequences deposited as Patent Deposit No. PTA-2182" in part (b). It is completely unclear what sequences were deposited in Patent Deposit No. PTA-2182; thus, it is unclear what the members of the group are. Applicant is reminded that only claims drawn to nucleic acids comprising SEQ ID NO:3 or encoding SEQ ID NO:4 are examined, and that they elected this invention without traverse.

Claims 15 and 25 are indefinite in their recitation of "highly stringent conditions" in part (f). It is not clear what hybridization conditions are considered highly stringent, given that the hybridization and wash times are not recited.

Claim 16 lacks antecedent basis for the limitation "isolated nucleic acid of claim 15" as claim 15 is drawn to a nucleic acid molecule.

Claims 19 and 24 lack antecedent basis for the limitation "isolated nucleic acids of claim 15" as claim 15 is drawn to a single nucleic acid molecule. Thus, the claims have an improper Markush group, because there is only member of the group.

It is unclear in claim 26 if the seed is transformed with the DNA construct the plant in claim 25 was transformed with or if it was transformed with another nucleic acid, as the construct will only be transmitted to half the progeny of the plant. It is suggested that --, wherein the seed comprises the DNA construct-- be inserted after "25".

Claim Rejections - 35 USC § 102

11. Claim 15 remains rejected under 35 U.S.C. 102(a) as being anticipated by Or et al (2000, GenBank Accession No. AF195867).The rejection is repeated for the reasons of record as set forth in the Office action mailed 13 March 2003. Applicant's arguments filed 16 June 2003 have been fully considered but they are not persuasive.

Applicant urges that this sequence and the instant sequence only have 46% identity and under the recited highly stringent conditions the two nucleic acids would not hybridize (response pg 16).

This is not found persuasive because hybridization and wash times are not recited. Furthermore, the claims drawn to a multitude of nucleic acids that hybridize to nucleic acids with 95% identity to SEQ ID NO:3, that encodes SEQ ID NO:4, or that are lipid transfer protein-encoding nucleic acids with 95% identity to SEQ ID NO:3. The nucleic acid taught by Or et al would hybridize to at least one of these, especially given the lack of recitation of hybridization and wash times.

12. Claims 15-20, 22 and 24-26 remain rejected under 35 U.S.C. 102(b) as being anticipated by Dixon et al (WO 98/51801). The rejection is repeated for the reasons of record as set forth in the Office action mailed 13 March 2003. Applicant's arguments filed 16 June 2003 have been fully considered but they are not persuasive.

Applicant urges that this sequence and the instant sequence only have 40.6% identity and under the recited highly stringent conditions the two nucleic acids would not hybridize (response pg 16).

This is not found persuasive because hybridization and wash times are not recited. Furthermore, the claims drawn to a multitude of nucleic acids that hybridize to nucleic acids with 95% identity to SEQ ID NO:3, that encodes SEQ ID NO:4, or that are lipid transfer protein-encoding nucleic acids with 95% identity to SEQ ID NO:3. The nucleic acid taught by Dixon et al would hybridize to at least one of these, especially given the lack of recitation of hybridization and wash times.

Conclusion

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, whose telephone number is (703) 308-5059. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at (703) 306-3218. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Customer Service at (703) 308-0198.

Anne R. Kubelik, Ph.D.
November 11, 2003